Centered on Molecules

The Vanderbilt University Center in Molecular Toxicology is one of nineteen NIEHS-supported Environmental Health Sciences Centers throughout the United States. Its primary purpose is to enhance individual and collaborative toxicology programs at Vanderbilt and nationwide. As scientists uncover how chemicals can cause damage to people at the molecular level, they will be able to develop techniques for screening for individual genetic susceptibility to environmental toxins and for effective preventive measures to protect human health. A hallmark of the Vanderbilt center is its interdisciplinary approach to understanding toxicological problems from the biochemical perspective and investigating questions related to toxicity at the molecular level.

CENTER IN MOLECULAR TOXICOLOGY
Vanderbilt University
School of Medicine

Center in Molecular Toxicology

Center of the center. Most of the Center in Molecular Toxicology's core groups are located in the Medical Research Building I, on the campus of Vanderbilt University.

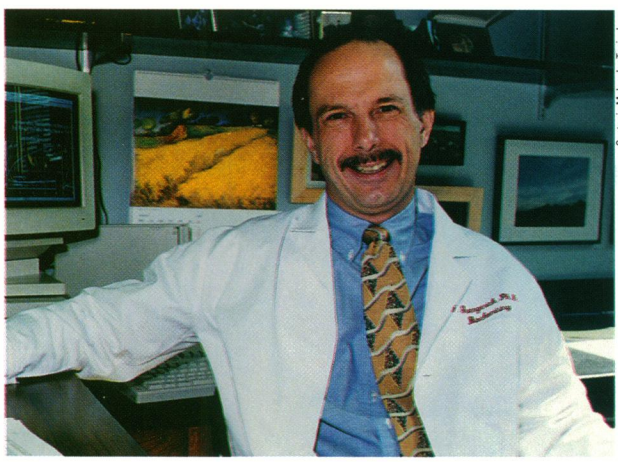
The Vanderbilt School of Medicine has been in the vanguard of research on cancer-causing substances since the Division of Toxicology was founded in 1967 in the Department of Biochemistry under the direction of the late Frank R. Blood. At its inception, the mission of the Division of Toxicology was the coordination of research and teaching related to harmful substances in foods such as chemical additives, naturally occurring toxins, and residues from agricultural pesticides and packaging materials. The division's success led to the establishment of the Vanderbilt Center in Environmental Toxicology under the auspices of an NIH Environmental Health Sciences grant in 1969. Over the years, the program has become increasingly interdisciplinary, with faculty in the departments of biochemistry, cell biology, chemistry, medicine, pathology, and pharmacology. Research emphasis has broadened to encompass endogenous chemicals and synergistic deleterious effects resulting from combinations of different chemicals in the body, all of which may give rise to mutations and play a role in activating oncogenes and inactivating tumor suppressor genes. The name was changed to the Center in Molecular Toxicology in 1984 to reflect increasing specialization in areas of toxicology that use molecular methodologies to elucidate physiological and genetic changes due to environmental and biogenic toxins.

Structure

The Center in Molecular Toxicology is organized into administrative cores, service cores, research cores, and an outreach program. The administrative cores are responsible for a variety of tasks including coordinating the toxicology seminar series and an annual visit by the External Advisory Group, processing applications, writing manuscripts and grants, and managing computer databases. The editorial office of the American Chemical Society's journal, *Chemical Research in Toxicology,* is also located at the center.

The service cores provide a full range of technological support and facilities necessary for molecular experimentation including NMR spectrometry, mass spectrometry, molecular biology, cell biology, and protein chemistry. The NMR and mass spectrometry facilities include state-of-the-art instrumentation for high-resolution analysis of biological macromolecules, which are critical in analytical chemistry for characterization of oligonucleotides and natural and synthetic molecules. The cell biology core provides human tissue and cell cultures, as well as monoclonal antibodies for biological studies. The protein chemistry core provides amino acid analysis and sequence determination of peptides, and the molecular biology core provides recombinant DNA technologies such as automated DNA synthesis and amplification.

There are seven core areas of research: enzymatic oxidation and conjugation, oxidative damage, DNA damage and mutagenesis, regulation of gene expression, analytic method development, neurotoxicology, and clinical toxicology.



Center in Molecular Toxicology

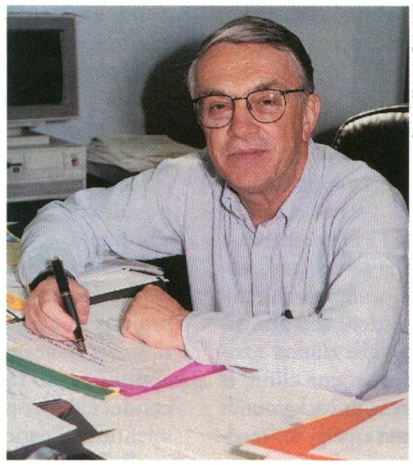
F. Peter Guengerich

Enzyme Bioactivation of Toxic Chemicals

The proteins, lipids, and sugars that make up a major part of foods, as well as other chemicals entering the body such as drugs or xenobiotics, are broken down by enzymes into smaller molecules before cells either use or eliminate them. Cells oxidize molecules through a series of enzyme-mediated reactions. Different environmental chemicals interact with enzymes in the body in various ways to alter normal biological processes. Certain enzymes in the liver catalyze detoxication reactions in which water-insoluble drugs and xenobi-

otics, which would otherwise cause cellular damage by becoming permanently attached to cell membranes or DNA, are made water-soluble and removed from the body by urine.

Center Director F. Peter Guengerich has pioneered investigation of the enzyme cytochrome P450, a primary catalyst involved in the oxidation of drugs, steroid hormones, and carcinogens. According to Guengerich, "There are over forty different kinds of P450 in the human body. The ones I am most interested in are the ones that act on chemicals that are not normally found in the human body (xenobiotics). We are trying to understand how enzymes detoxify drugs and carcinogens and how these same enzymes can also make them more active."



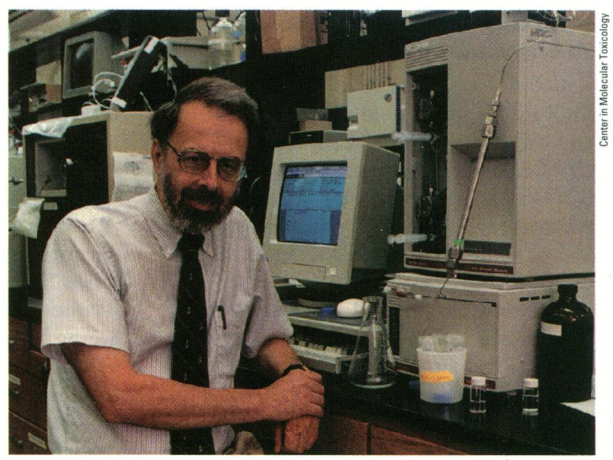
Center in Molecular Toxicology

Michael R. Waterman

A major contribution to this understanding was Guengerich's characterization of how P450 converts aflatoxin—a natural chemical produced by a fungus that grows on rice, peanuts, and corn—into a potent carcinogen when ingested. Human populations in Africa and China, countries that lack adequate inspection of agricultural products, have unusually high rates of liver cancer caused by aflatoxin. Guengerich and colleagues at Vanderbilt identified a particular P450 enzyme involved in aflatoxin bioactivation. Thomas Harris, associate director of the center, synthesized the active form of aflatoxin, a potent epoxide that sticks to DNA, and has done most of the center's chemical experimentation on this molecule.

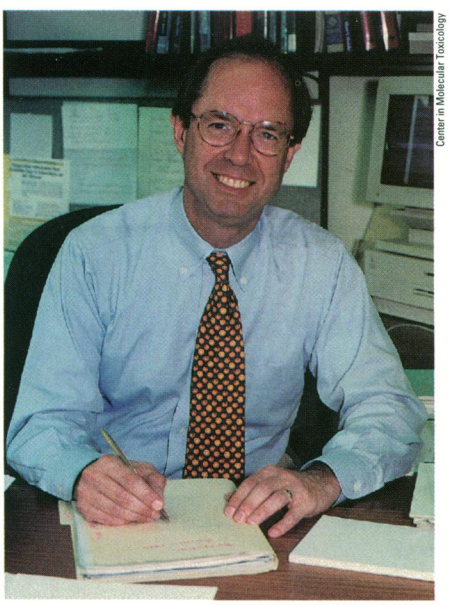
Guengerich is currently collaborating with scientists at Johns Hopkins University to investigate the role of a newly discovered cytochrome that is found in high concentrations in the breast, uterus, ovaries, and prostate gland, and that may play a role in cancers in the human reproductive system. An important objective of this research is to delineate the steps in initiation of P450 carcinogenic activity in order to design effective drug therapies that can be used to prevent enzyme-mediated cancers.

Working with Michael R. Waterman, professor and chairman of biochemistry, Guengerich has genetically engineered *E. coli* bacteria with human P450 genes that express high levels of the newly discovered enzymes. Human cytochrome P450s have also been engineered directly into the Ames *Salmonella* tester strain for genotoxicity, which has practical application for screening mutagenic effects of chemicals activated by human enzymes. The bacterial expression system will also be a valuable tool in site-directed mutagenesis studies.



Center in Molecular Toxicology

Thomas Harris



Center in Molecular Toxicology

Lawrence J. Marnett

DNA Damage from Endogenous Chemicals

Research in the A.B. Hancock, Jr., Memorial Laboratory for Cancer Research, directed by Lawrence J. Marnett, has shown considerable DNA damage may be caused by endogenous chemicals produced during the body's normal metabolic processes. Marnett says, "The scientific community originally thought that it was only chemicals in the environment [that caused damage]. We now know that our own bodies damage our DNA through normal processes." Marnett is particularly interested in enzymes that catalyze the conversion of polyunsaturated fatty acids to bioactive lipids such as prostaglandin. These fatty-acid derivatives bind to different cell-surface receptors and have various biological effects including smooth muscle contraction and inflammation. DNA adducts can be formed from lipid oxidation products. Marnett is investigating the biological consequences of the adherence of endogenous chemicals produced by lipid biosynthesis to DNA, and how such chemicals act as internal mediators to initiate mutations and tumors in human tissues. Certain byproducts of lipid oxidation are of particular concern because they have been implicated in tumor metastasis. Approaches to studying the causes and effects of DNA damage being used in Marnett's lab include measuring the amount of damage to DNA, and creating synthetic DNA molecules that have been damaged in various ways to use as models. "We try to introduce the damage to a specific site and then observe the effects of the damage," Marnett says. The findings of basic research promise to have practical benefits to health care by improving the ability to assess people at risk for different types of cancer. "The biggest impact our work can have is in human risk assessment," Marnett predicts. "We will have a better concept of what is causing cancer in people, and, therefore, will soon be better able to determine who is at risk for certain types of cancer."

Aspirin-Enzyme Link

Many cancers are caused by oxidative stress. A recent discovery revealed that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) function by blocking enzymes involved in the lipid oxidation process to prevent formation of harmful, biologically active intermediates. Comparing cancerous tissue and healthy tissue from 28 patients who underwent surgery for colon cancer, Raymond N.

Center in Molecular Toxicology

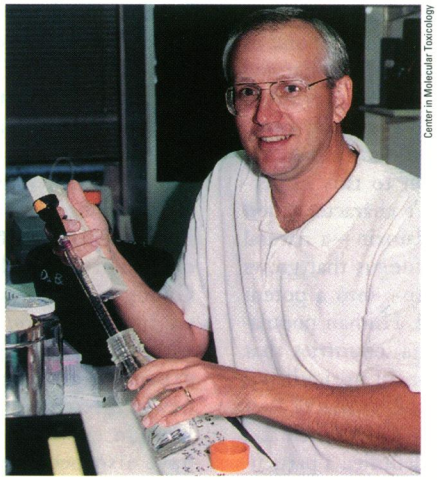
Timothy Meredith

DuBois, an associate professor of medicine and cell biology, found unusually high levels of one such enzyme, cyclooxygenase-2 (COX-2), in cancerous colon tissue, whereas levels in healthy tissue were very low or undetectable. COX-2 leads to production of prostaglandin and other biogenic chemicals linked to cancer. It has been shown that arthritis patients who take NSAIDs regularly have a 50% reduction in risk for developing colon cancer. Colorectal cancer is one of the leading causes of cancer mortality; approximately 150,000 people are diagnosed with colon cancer and over 50,000 die from the disease each year. DuBois is investigating how aspirin inhibits COX-2 activity and thereby reduces cancer risk. Understanding the enzyme blocking mechanism can lead to better diagnostic and screening strategies, as well as development of highly specific, targeted therapies for the prevention of intestinal tumors.

Outreach

An important part of the center's outreach program is the Clinical Toxicology Center, which includes the Middle Tennessee Poison Center (MTPC). The MTPC comprises a clinical toxicology admitting service and outpatient clinic service, an occupational and environmental medicine section, and analytical toxicology laboratories. The clinical toxicology admitting and outpatient clinic is staffed by faculty members with backgrounds in internal, occupational, and emergency medicine. It is the only such service in Tennessee and one of three nationwide. "The addition of clinical toxicology at Vanderbilt is a tremendous opportunity," said Guengerich of the MTPC. "It should be one of the premier programs of its type in the nation and should complement our existing strengths in molecular programs."

The MTPC program, directed by the Center in Molecular Toxicology's Timothy Meredith, serves 57 counties in Tennessee, covering a population of approximately 3 million. The MTPC is now extending the original primary service of prevention and management of poisoning due to household chemicals and drugs to include exposure to environmental chemicals. The MTPC is establishing an environmental chemicals "hotline" to answer questions about adverse health effects from exposure to environmental chemicals, and is developing an interactive database focused on environmental chemicals and health-related problems. The database will be accessible on-line via the World Wide Web at http://www.toxicology.mc.vanderbilt.edu.



Center in Molecular Toxicology

Raymond N. DuBois

Training in toxicology at the center extends from undergraduate to graduate, postdoctoral, and medical students. In addition to formal courses and seminars on toxicology, students are offered the opportunity to participate in ongoing research projects to gain skills essential to investigations in molecular toxicology and clinical applications. Two monthly seminars are conducted by center faculty and by outside scientists of national renown.

Reflecting on its past history and looking toward the future of the Center in Molecular Toxicology, Guengerich says, "Over the years, our center has been able to develop by emphasizing high quality science, and we've been able to assemble an outstanding group of individuals. There is considerable strength in chemistry and carcinogenesis, and some of the new directions such as neurotoxicology and gene regulation should enhance our overall scientific program." As scientists like those at the center carry on their work, they are charting new courses for delivering improved health care, enhancing human risk assessment, and solving modern environmental health problems.

Mary Eubanks

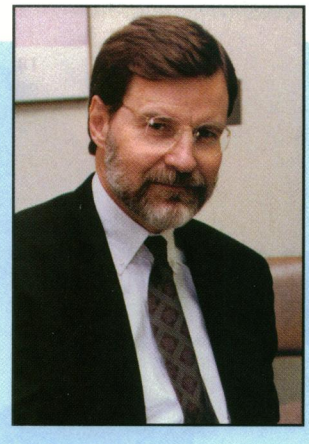
Visit the Center in Molecular Toxicology on the Web!

http://www.toxicology.mc.vanderbilt.edu/

The Center provides an environment for research efforts in molecular toxicology by investigators and affiliated faculty in biochemistry, cell biology, chemistry, medicine, pathology, and pharmacology.

The site provides information on the center's research and service cores, study and training, center investigators and affiliates, community outreach and education, and a calendar of events.

Wilson Named Deputy Director



Steve McCaw, Image Associates

On September 1, Samuel H. Wilson, an expert in the fields of environmental toxicology and genetic enzymology, will join the NIEHS as its new deputy director. Wilson will be responsible for helping Director Kenneth Olden administer the NIEHS, which employs over 850 people and has an annual budget and pass-through funds of approximately $365 million. Wilson said that he sees the position as an opportunity to "stimulate and foster outstanding research nationally in environmental health science and to make enhanced use of the research strengths [at the institute]."

Wilson emphasized that increased partnership and interaction between the academic community and industry would be necessary to achieve these goals. Increased cooperation will allow research to progress more efficiently, Wilson said, and will be beneficial to both sectors. "These relationships can be facilitated by NIEHS," he said.

Wilson also said he would like to see the NIEHS place more emphasis on the development of new research technologies. "We need to take advantage of new advances in molecular genetics to help us better understand the impact of environmental exposure on health," Wilson said. As an example of how such technologies could advance the field of environmental health, Wilson cited the use of genetically engineered bacteria and animals as sentinels for detecting toxicants.

A world-recognized authority on DNA polymerases, Wilson brings with him extensive knowledge and experience in genetics and toxicology. Currently at the University of Texas Medical Branch at Galveston, Wilson is the founding director of the Sealy Center for Molecular Science and holds the Mary Gibbs Jones Distinguished Chair in Environmental Toxicology. He also serves as director of the Centennial Center for Environmental Toxicology and is a professor in the Department of Human Biological Chemistry and Genetics.

Before his University of Texas appointment, Wilson was chief of the Nucleic Acid Enzymology Section at the National Cancer Institute's Laboratory of Biochemistry in Bethesda, Maryland. His career with NCI, a sister institute of the NIEHS, began in 1970. Since that time, Wilson's pioneering research in the field of genetic enzymes, which are responsible for replication and repair of genomic DNA, has led to a much greater understanding of how these enzymes function. His work could eventually enable scientists to design drugs that control replication of cancer cells or viral replication within HIV-infected cells.

Wilson received his M.D. from Harvard Medical School in 1968. He received postdoctoral training at Dartmouth Medical School and the National Institutes of Health. "With the appointment of Dr. Wilson, the institute is gaining the benefit of an outstanding researcher and science administrator," Olden said.